UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/250,883	02/16/99	RUSSELL J	6131.US.02

023492
ABBOTT LABORATORIES
DEPT. 377 - AP6D-2
100 ABBOTT PARK ROAD
ABBOTT PARK IL 60064-6050

HM12/0410

EXAMINER	
MYERS, C	
ART UNIT	**PAPER NUMBER**
1655	15

DATE MAILED: 04/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/250,883	Applicant(s) RUSSELL ET AL.	
	Examiner Carla Myers	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,13-20 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9, 13-20, 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

1. This action is in response to Paper No. 13, filed January 11, 2001. Applicants arguments have been fully considered but are not persuasive to overcome all grounds of rejection. Any rejections not reiterated herein are withdrawn. This action is made final.

2. The following constitutes new grounds of rejection:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 9, 13-20 and 24 are rejected under 35 U.S.C. 101 because the claimed invention lacks a credible, substantial, specific or well-established utility.

The claims are drawn to polynucleotides having at least 90% identity with any one of SEQ ID NO: 1-14. The claimed polynucleotide are not supported by either a specific and substantial asserted utility or a well-established utility. The specification fails to provide objective evidence of any activity for the claimed polynucleotide or to show that polynucleotide having the stated consensus sequence of SEQ ID NO: 14 even exist. The specification teaches that a consensus sequence derived from SEQ ID NO: 1-13 hybridizes to ESTs in 27% of breast tissue samples, whereas the consensus sequence only hybridizes to ESTs in 3.4% of non-breast tissue samples. Based on this information, the specification concludes that the individual sequence fragments of SEQ ID NO: 1-13 and the consensus sequence of SEQ ID NO: 14 are useful in "detecting, diagnosing, staging, monitoring, prognosticating, preventing or treating or determining the predisposition to, disease and conditions of the breast, such as breast cancer" (see page 10 of the

specification). However, the specification provides absolutely no evidence that the sequences of SEQ ID NO: 1-14 are correlated with any type of disease or condition of the breast. There is no information provided in the specification regarding the level of expression of SEQ ID NO: 1-14 in any type of diseased breast tissue. The finding that mRNAs which hybridize to SEQ ID NO: 14 are more prevalent in breast tissue than in normal tissue does not indicate that such sequences are associated with diseases or conditions of the breast. Furthermore, the finding that mRNAs which hybridize to SEQ ID NO: 14 are more prevalent in breast tissue rather than normal tissues does not indicate that mRNAs which hybridize to any one of SEQ ID NO: 1-13 are also more prevalent in breast tissue because there is no evidence concerning the hybridization properties of the individual nucleotide fragments. Furthermore, the claims as written are inclusive of all nucleic acids having 90% identity with SEQ ID NO: 1-14, and thereby includes allelic variants of SEQ ID NO: 1-14 having different functional properties that those associated with SEQ ID NO: 1-14. The specification does not disclose a single nucleic acid having 90% identity with any of SEQ ID NO: 1-14 and does not exemplify any conditions or diseases associated with any species in the genus of nucleic acids having 90% identity with SEQ ID NO: 1-14. The specification suggests that the claimed polynucleotide could be used for therapeutic purposes. Clearly, further research would be required to identify a disease for which the protein encoded by SEQ ID NO: 1-14 is involved and for which treatment with SEQ ID NO: 1-14 or any nucleic acid having 90% identity with SEQ ID NO: 1-14 would be effective or for which detection of SEQ ID NO: 1-14 expression would be informative. As stated in Brenner v. Manson, 383 U.S. 519 535-536, 148

USPQ 689, 696 (1966) " a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion". Support for an asserted utility that is specific and substantial would require, for example, a showing of a particular function for an encoded polypeptide. Merely identifying and studying the properties of a polypeptide or the diseases in which a polypeptide or polynucleotide may be involved does not constitute a "real world" context of use. Moreover, the use of the claimed polynucleotide to detect breast tissue is considered to be a general use, rather than a specific use since tissue specific expression is a characteristic of a large genus of nucleic acids. Accordingly, the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility. Applicants attention is drawn to the Revised Interim Utility Guidelines set forth in the Federal Register, December 21, 1999. Vol. 64, No. 244, pages 71427-71440.

3. Claims 9, 13-20 and 24 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial, or credible asserted utility or well-established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

Furthermore, with respect to the breadth of the claims, the claims are inclusive of polynucleotide having at least 90% identity with SEQ ID NO: 1-14. The claims further encompass polynucleotide which encode for at least one epitope. It is also noted that the claims have been amended to delete the reference to a "BS203" polynucleotide. However, the claimed polynucleotide have been defined in the specification only in terms of the fact that they are BS203

polynucleotide or comprise fragments of BS203 polynucleotide. Accordingly, deleting the term "BS203" from the claims does not change the definition of SEQ ID NO: 1-14 provided in the specification. The specification discloses a single polynucleotide having the consensus sequence of SEQ ID NO: 14 wherein said polynucleotide was constructed by overlapping contiguous clones isolated from breast tissue wherein said clones consist of the sequences of SEQ ID NO: 1-13. While the specification has constructed a single polynucleotide expressed in human breast tissue by determining the consensus sequence of overlapping cDNA clones, the specification has not identified any variants or homologs of this polynucleotide. It is unclear from the specification as to what would be considered to be the functional and/or structural properties of a polynucleotide consisting of SEQ ID NO: 1-14 or a polynucleotide having 90% identity with SEQ ID NO: 1-14. No specific guidance has been provided in the specification as to how to reasonably isolate additional BS203 polynucleotide without undue experimentation. It is well established that to claim a chemical compound, such as a polynucleotide, the inventor must be able to define the compound so as to distinguish the compound from other materials and the inventor must clearly define the compound in terms of structure and/or function (e.g. nucleic acid sequence, length of nucleic acid, specific functional activity of nucleic acid) so as to provide a permanent and definite idea of the complete and operative invention. Without a clear and fixed definition of the claimed invention, the skilled artisan cannot make and use that invention without undue experimentation. In the instant case, the specification has not clearly defined the functional activities of what is intended to be encompassed by molecules having the sequence of

SEQ ID NO: 1-14. Secondly, claims 15 and 24 are directed to polynucleotide which comprise a sequence encoding at least one epitope. Yet, the specification does not identify any epitopes and no guidance is provided as to how one of skill in the art would select appropriate fragments of a protein which function as an epitope. In view of the lack of disclosure in the specification as to portions of the SEQ ID NO: 1-14 which would encode for epitopes and in view of the lack of guidance provided in the specification as to how to select nucleic acids which would encode suitable epitopes, undue experimentation would be required for one of skill in the art to successfully identify nucleic acids that could be used to synthesize BS203 epitopes. Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the specification has identified 13 fragments of a BS203 nucleic acid and one consensus BS203 nucleic acid (i.e., SEQ ID NO: 14), yet the scope of the claims encompasses nucleic acid variants having distinct functional activities as compared to those of SEQ ID NO: 1-14.

RESPONSE TO ARGUMENTS

In the response filed January 11, 2001, Applicants traverse this rejection by stating that the claimed sequences are members of a RING finger family. The response states that "Recently a new class of zinc-finger proteins was identified and designated as the RING finger family". Applicants cite Borden, Saurin, Regnier and Moilanen as teaching proteins that are members of the RING finger family and state that some members of this family have "oncogenic associations". Applicants assert that SEQ ID NO: 17 contains a RING finger motif which differs from the prototype RING finger motif only in that BS203 (SEQ ID NO: 17) contains one residue rather than two residues between the first two cysteine residues of the RING finger motif. It is further noted that BS203 is a member of a subfamily of RING finger proteins called the tripartite subgroup which is characterized by three domains, including the RING finger, the B box, and the coiled-coil domain. Applicants assert that BS203 contains a B box and coiled-coil domain in addition to the RING finger domain. Thereby, Applicants conclude that BS203 is a member of the RING finger family of proteins and that the claimed polynucleotide have utility as encoding RING finger proteins. This argument has been fully considered but is not persuasive because the specification as originally filed does not characterize the claimed nucleic acids as encoding a RING finger protein. Therefore, the specification as originally filed did not teach one of skill in the art to use the disclosed nucleic acids to encode RING finger proteins and does not teach how to select and use variants having 90% identity with SEQ ID NO: 1-14 based on said molecules having the property of encoding a RING finger protein. Furthermore, the fact that the claimed

nucleic acids encode for proteins having domains known to be present in RING finger proteins does not indicate that the claimed nucleic acids encode for proteins having the same functional properties as the RING finger proteins in the prior art. No evidence has been provided in the specification to show that any of the claimed nucleic acids or nucleic acids having 90% identity thereto encode for proteins having any functional activity and particularly no evidence has been provided to show that the claimed nucleic acids encode for proteins having the functional activity of a RING finger protein. There is also no evidence to support the contention that the difference in the RING finger motif of BS203 compared to the consensus RING finger motif do not affect the activity of the RING finger protein. In addition, identifying domains within a new protein which are conserved with other known proteins, does not indicate what specific function the new protein might have. That is, while other proteins having RING finger domains have been characterized and some have been found to be "associated" with cancer, this information does not provide evidence that all proteins having a RING finger domain are also associated with cancer or that BS203 will have the same functional activity as that of any other member in the RING finger family of proteins. No factual evidence has been provided to show that the instantly claimed nucleic acids are correlated with cancer and could be used for the diagnosis of cancer or that the claimed nucleic acids have the same activity as any particular RING finger protein. Moreover, with respect to variants thereof, it is well accepted that even a single nucleotide or amino acid change or mutation can destroy the function of an encoded protein. In the absence of evidence characterizing the structural and functional components of a protein, the effects of these changes

are largely unpredictable. In particular, it is unpredictable as to which changes will have a significant effect on activity or structure and which changes will be silent. The specification as originally filed does not provide any information regarding changes that may be made in the disclosed nucleic acids and encoded proteins without altering the biological properties of these molecules.

Applicants further argue that expression of BS203 is highly tissue specific. Applicants provide a 132 Declaration by Dr. Paula Friedman showing that BS203 is approximately 22 times more abundant in breast tissue than in the rest of the body. However, nucleic acids which are expressed primarily in normal breast tissue constitute a large class of molecules. Accordingly, breast specific expression of BS203 is considered to be a general utility, rather than a specific utility. Applicants assert that "Gene products, such as messenger RNA (mRNA), that code for a particular protein that are more prevalent and highly specific to a given tissue are extremely useful as a marker for detection of disease in that tissue". Applicants conclude that because BS203 is highly expressed in breast tissue, that it is useful as a "diagnostic marker for diseases of the breast". However, diagnosis of any disease of the breast is considered to be a general utility, rather than a specific and substantial utility. Furthermore, there is no evidence of record to show that expression of BS203 is correlated with any particular disease of the breast. Differential expression of BS203 does not indicate that this nucleic acid can be used to diagnose any particular disease. The use of BS203 to diagnose any disease of the breast is a utility that applies to a broad class of inventions. The general concept of using a biomolecule for diagnostic

purposes in the absence of a disclosure of a particular association between the biomolecule and a specific disease does not meet the 101 requirements for a showing of a specific, substantial and credible utility. As stated *In re Kirk*, 153 USPQ48, 53 (CCPA 1967), "We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this relates".

With respect to the use of BS203 as a marker of breast cancer, Applicants have provided no evidence that BS203 is differentially expressed in breast cancer as opposed to normal breast tissue. Applicants response and the 132 Declaration of Dr. Paula Friedman state that PSA and CEA are tissue-specific protein markers which are useful for diagnosing cancer. It is stated that the tissue specific expression of PSA and CEA is similar to that of BS203. It is also pointed out that extracelluar expression of PSA and CEA are correlated with prostate and colon cancer, respectively. Because of these similarities in tissue specific expression, Applicants conclude that "the presence of BS203 outside of the breast illustrates cancer development of that tissue". However, Applicants have provided absolutely no evidence to show that BS203 is found "outside of the breast", i.e. in blood, stool or urine or that BS203 protein is expressed extracellularly. Based on Applicants arguments, one would assume that all proteins that are highly expressed in a

given tissue, would also be extracellularly expressed. However, Applicants have provided no evidence to support such a general contention. In fact, there is no clear association established in the art between levels of protein expression in a tissue and the ability of that protein to be expressed extracellularly. There is also no evidence to support the contention that all proteins that are highly expressed in a given tissue are associated with causing disease. Rather, over-expression of tissue specific proteins is often associated with a protective function. Thus, while BS203 may be highly expressed in breast tissue, this finding does not provide evidence regarding the extracellular expression of BS203, the shedding of breast cells containing BS203 into blood, urine, or stool, or an association between BS203 levels and the occurrence of cancer. Applicants assertions regarding BS203 expression "outside of the breast" are speculative at best and Applicants statement that "the presence of BS203 outside of the breast illustrates cancer development of that tissue" is misleading since no evidence has been providing to show that BS203 has in fact been detected "outside of the breast". Applicants state that they have shown a credible utility for the claimed polynucleotide and should not be held to the extraordinarily high threshold improperly held by the Examiner. However, Applicants have not shown that the claimed polynucleotide have either a specific or substantial asserted utility or a well established utility. In order for a polynucleotide to be useful for the diagnosis of disease, there must be a well-established or disclosed correlation between the claimed polynucleotide and the disease. The presence of the BS203 polynucleotide in normal breast tissue is not sufficient to establish that

overexpression of BS203 is causative of or diagnostic of any disease of the breast, particularly breast cancer.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

April 9, 2001

Carla Myers

CARLA J. MYERS
PRIMARY EXAMINER